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PRACTICE

GUIDELINES

Prevention and management of neutropenic sepsis in patients with cancer: summary of NICE guidance

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This is one of a series of *BMJ* summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Neutropenic sepsis is a potentially fatal complication of treatment for cancer, with mortality rates of 2-21%.¹ An investigation by the National Confidential Enquiry into Patient Outcome and Death and a follow-up report by the National Chemotherapy Advisory Group highlighted problems in the management of neutropenic sepsis in adults receiving chemotherapy.^{2,3} The problems included inadequate management of neutropenic sepsis leading to avoidable deaths, and the lack of systems for urgent assessment and of policies at organisation level for dealing with neutropenic sepsis. This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on the prevention and management of neutropenic sepsis in patients of any age with cancer.⁴

Recommendations

NICE recommendations are based on systematic reviews of the best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italic in square brackets.

Information and support for patients and carers

- Provide patients having anticancer treatment and their carers with written and verbal information, before starting and throughout their cancer treatment, on:
 - Neutropenic sepsis

- How and when to access 24 hour specialist oncology advice

- How and when to seek emergency care.

[Based on the experience and opinion of the Guideline Development Group (GDG)]

Training for healthcare professionals

- Provide training on the identification and management of neutropenic sepsis to all healthcare professionals likely to be involved in the management of patients having cancer treatment. [Based on the experience and opinion of the GDG]

Reducing the risk of septic complications of anticancer treatment

- For adult patients (aged ≥ 18 years) with acute leukaemias, stem cell transplants, or solid tumours in whom clinically significant neutropenia (neutrophil count $\leq 0.5 \times 10^9/L$) is an expected consequence of chemotherapy, offer prophylaxis with a fluoroquinolone only during the expected period of neutropenia. The lack of data for children and young people and for patients with lymphomas, makes it impossible currently to recommend the use or avoidance of a fluoroquinolone during periods of neutropenia. [Based on moderate to high quality evidence from systematic reviews and meta-analyses of randomised controlled trials]
- Centres where patients are receiving fluoroquinolones for antibiotic prophylaxis of neutropenic sepsis should monitor rates of antibiotic resistance. [Based on the experience and opinion of the GDG]

- Do not routinely offer granulocyte colony stimulating factor to prevent neutropenic sepsis in adults having chemotherapy unless they are receiving this as an integral part of the chemotherapy regimen or to maintain dose intensity. *[Based on high quality evidence from systematic reviews and meta-analyses of randomised controlled trials and de novo economic analysis]*

Outside these indications, the role of granulocyte colony stimulating factor in the treatment of patients with cancer is highly controversial. An economic analysis undertaken specifically for the guideline showed that the use of granulocyte colony stimulating factor when given solely to prevent neutropenic sepsis was highly unlikely to be cost effective.

Referral guidance

- Suspect neutropenic sepsis if patients having cancer treatment become unexpectedly or seriously unwell.
- Refer patients with suspected neutropenic sepsis immediately for assessment at their appropriate local hospital.

[Both points are based on the experience and opinion of the GDG]

Emergency treatment and assessment

Suspected neutropenic sepsis is an acute medical emergency.

- Start immediate empirical antibiotic treatment. *[Based on the experience and opinion of the GDG]* The current National Cancer Action Team's guidance and measures for cancer services suggest that treatment should be started within one hour.⁵
- Use monotherapy (the combination piperacillin with tazobactam) as initial empirical antibiotic treatment, and do not prescribe additional aminoglycoside(s), unless there are patient specific or local microbiological indications, such as a high rate of resistance to piperacillin with tazobactam. *[Based on high quality evidence from systematic reviews and meta-analyses of randomised controlled trials]*
- Do a full clinical assessment of patients, including:
 - History and examination
 - Full blood count, and kidney and liver function tests (including albumin)
 - C reactive protein, lactate and blood culture
 - Additional peripheral blood culture, if possible, in patients with a central venous access device to improve the detection rates for bacteraemia
 - Urinalysis in all children aged ≤ 5 years.

[Based on low quality evidence from observational studies and the experience and opinion of the GDG]

- Do not do chest radiography unless clinically indicated. *[Based on low to moderate quality evidence from observational studies]*
- Do not prescribe empiric glycopeptide antibiotics to patients with neutropenic sepsis and a central venous access device. *[Based on very low or low quality evidence from systematic reviews of randomised controlled trials]*
- Do not remove the central venous access device as empirical management. However, it may require removal if it is suspected to be the focus of uncontrolled infection.

[Based on very low or low quality evidence from observational studies]

Confirming the diagnosis

- Diagnose neutropenic sepsis in every patient whose temperature is $>38^{\circ}\text{C}$ and neutrophil count $<0.5 \times 10^9/\text{L}$. *[Based on low quality evidence from observational studies]*

Assessing the patient's risk of septic complications

- An oncology specialist should assess every patient's risk of septic complications within 24 hours, using a validated risk scoring tool. *[Based on moderate quality evidence from systematic reviews of observational studies]*

No clear evidence describes the superiority of one system over another. The box describes two commonly used systems: the Multinational Association for Supportive Care in Cancer (MASCC) score (for adults) and a modified Alexander rule (for children and young people).^{6 7}

Patients at low risk of septic complications

- Consider treating patients at low risk of developing septic complications with outpatient antibiotic treatment, if clinically appropriate and their domestic circumstances will allow them to return to hospital promptly if a problem develops. *[Based on moderate quality evidence from systematic reviews]*

Patients at high risk of septic complications

- Review and repeat the risk assessment daily while the patient is an inpatient, using the validated risk scoring tool. *[Based on the experience and opinion of the GDG]*
- Switch from intravenous to oral antibiotic treatment after 48 hours in patients who are reassessed as being at low risk of septic complications, and discharge them home if clinically appropriate and domestic circumstances allow. *[Based on low to moderate quality evidence from randomised trials]*
- Discontinue empirical antibiotic treatment in patients who have clinically responded to treatment—for example, by defervescence and an absence of signs of infection, irrespective of neutrophil count. *[Based on low quality evidence from observational studies]*
- Continue inpatient empirical antibiotic treatment in patients who have unresponsive fever unless an alternative cause of fever is likely. *[Based on the experience and opinion of the GDG]*
- Do not change primary empirical antibiotics in patients with unresponsive fever unless there is clinical deterioration or a specific microbiological indication. *[Based on low quality evidence from randomised trials]*

Overcoming barriers

Teenagers and young adults with cancer seem to be twice as likely to die of neutropenic sepsis as other age groups,⁴ and the Guideline Development Group urges those who care for these patients to emphasise to them the life threatening nature of this condition. The recommendation not to use granulocyte colony stimulating factor to prevent episodes of neutropenia challenges conventional practice; however, granulocyte colony stimulating

Commonly used, validated risk assessment tools for neutropenic sepsis*Multinational Association for Supportive Care in Cancer (MASSC) score for adults⁶*

Calculate the score for each patient at admission, according to the factors and scores listed below. If the total score is 21 or higher, they are at low risk of severe septic complications.

- Solid tumour or lymphoma with no previous fungal infection = 4
- Outpatient status (at onset of fever) = 3
- Age <60 years = 2
- Burden of illness:
 - No or mild symptoms = 5
 - Moderate symptoms = 3
 - Severe symptoms = 0
- No hypotension (systolic BP >90 mmHg) = 5
- No chronic obstructive pulmonary disease = 4
- No dehydration = 3

Modified Alexander rule for children and young people <18 years old⁷

Patients are at low risk of septic complications if:

- They are not having treatment for acute myeloblastic leukaemia or Burkitt lymphoma, or the induction phase of treatment for acute lymphoblastic leukaemia; do not have a progressive disease; or are not having treatment for relapsed disease with marrow involvement; or
- They do not present with any of the following features: hypotension, tachypnoea or hypoxia <94%, new changes in chest radiography results, altered mental status, severe mucositis, vomiting or abdominal pain, focal infection, other clinical reason(s) for inpatient treatment, neutrophil count <0.1 × 10⁹/L.

factor may be an integral part of the chemotherapy regimen or used to maintain dose intensity in some patients having chemotherapy with proved survival advantage. Clinicians may need to explain clearly their decisions to use granulocyte colony stimulating factor to healthcare commissioners. Effective monitoring and hospital-wide asepsis should mitigate potential problems such as antibiotic resistance patterns and *Clostridium difficile* from the increased use of prophylactic fluoroquinolone antibiotics; the GDG concluded from the available evidence that the potential disadvantage from this was outweighed by the reduction in mortality from neutropenic sepsis. Delivering care outside hospital to patients at low risk of septic complications will need careful implementation of early, risk stratified discharge together with informed community support to enable this to happen safely and improve the experience of patients.

The members of the Guideline Development Group were Barry W Hancock, Robert Phillips, Wendy King, Barbara Anne Crosse, Mark Holland, Catherine Oakley, Rosemary A Barnes, Anne Higgins, Peter Jenkins, Anton Kruger, Paul D Wallman, Jeanette Hawkins, Helen Clayson, Miranda Holmes, Anne Davidson, Janie Thomas, Nicola Harris, Rachel Drew. The members of the guideline team at the National Collaborating Centre for Cancer were John Graham, Andrew Champion, Angela Bennett, Lianne Gwillim, Nathan Bromham, Karen Francis, Mia Schmidt-Hansen, Catrin Lewis, Sabine Berendse, Stephanie Arnold Huajie Jin, Alec Miners, and Timothy Simmons. The members of the NICE project team were Sharon Summers-Ma, Claire Turner, Anthony Gildea, Judith Thornton, Jasdeep Hayre, and Judy McBride.

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Further information on the guidance

There are many local, regional, national, and international guidelines on the management of neutropenic sepsis, and great variation in practice in the United Kingdom.⁴ Few of these guidelines focus on the management of neutropenic sepsis in the NHS setting, and none has explicitly examined the cost effectiveness of their recommendations. This NICE guideline was developed to reduce unwarranted variation in service provision and bring into practice the most cost effective approaches to prevention and management of neutropenic sepsis. The recommendations were developed after discussion of the relevance of the evidence to children, young people, and adults and are intended for use in patients of any age with cancer. Where the guideline gives age limited or disease specific recommendations these are clearly indicated as such.

Methods

This guidance was developed by the National Collaborating Centre for Cancer using methods from NICE's standard processes (www.nice.org.uk/guidelinesmanual). The guidance review involved literature searches to identify relevant evidence, with critical appraisal of the quality of the identified evidence. A multidisciplinary team (the Guideline Development Group (GDG)) of service users, carers, and healthcare professionals was established to review the evidence and develop the subsequent recommendations. The healthcare professionals in this team included medical and clinical oncologists, haematologists, a microbiologist, an emergency medicine physician, paediatricians, an adult acute medicine physician, and chemotherapy, paediatric, community, and haematology specialist nurses. The guidance then went through an external consultation with stakeholders. The GDG considered the stakeholders' comments, reanalysed the data where necessary, and modified the guidance as appropriate.

NICE has produced three different versions of the guidance: a full version; a summary version known as the "NICE guidance"; and a version for people using NHS services, their families and carers, and the public. All these versions are available from the NICE website. Updates of the guidance will be produced as part of NICE's guideline development programme.

Cost effectiveness analysis of the use of colony stimulating factors (particularly granulocyte colony stimulating factor) and antibiotics as prophylaxis in patients at risk of neutropenic sepsis

As neutropenic sepsis affects many patients and the use of colony stimulating factors and antibiotics carries potentially substantial differences in cost, the GDG had serious concerns about cost effectiveness. It conducted a systematic review of previous economic models, but all studies were deemed to be at most only partially applicable to the guideline and to have very serious or potentially serious limitations. Accordingly, the group constructed a de novo model, which examined the cost effectiveness of the use of fluoroquinolone antibiotics, colony stimulating factors, both, or neither, in the prevention of neutropenic sepsis for adults (age >18 years) with cancer who were being treated as outpatients and whose chemotherapy regimen did not include granulocyte colony stimulating factor (G-CSF).

Findings of the base-case economic analysis

At the NICE "willingness to pay" threshold of £20 000 (£25 000; \$31 000) per quality adjusted life year:

- For patients with a solid tumour who can take fluoroquinolone, primary prophylaxis with fluoroquinolone is the most cost effective prophylactic strategy
- For patients with a solid tumour who cannot take fluoroquinolone, no prophylaxis is the most cost effective strategy
- For patients with non-Hodgkin lymphoma or Hodgkin lymphoma, no prophylaxis is the most cost effective strategy.

All the results in the analysis were robust to both structural sensitivity analysis and probabilistic sensitivity analysis.

To test the health economic model the following scenarios were explored: 100% risk of neutropenic sepsis; 90% drug discount; five days of G-CSF per cycle; reduced daily dose of G-CSF. The one way sensitivity analysis showed that the model was robust to all scenarios, except if the effectiveness of fluoroquinolones versus nothing or placebo was reduced to a relative risk of ≥ 0.79 and if the cost of pegylated G-CSF was discounted to £179.50 or less per dose when pegylated G-CSF became cost effective.

Future research

The guideline recommends research to:

- Assess the benefits and disadvantages of different types of support, and information about neutropenic sepsis, for patients and their relatives
- Determine the value of symptoms and signs in patients in the community predicting neutropenic sepsis and its outcome
- Evaluate the effectiveness of very early (within 24 hours) discharge from hospital with oral antibiotics for patients with neutropenic sepsis
- Investigate the cost effectiveness of prophylaxis of neutropenic sepsis with antibiotics and/or granulocyte colony stimulating factor preparations in children and young people, and in adults with lymphoma, receiving cancer treatment
- Determine the incidence of suspected and proved neutropenic sepsis in a prospective national cohort study